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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/879,217	06/13/2001	Kathleen Danenberg	11220/129	6207

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/879,217	DANENBERG, KATHLEEN6	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14,16,23-25 and 27-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14,16,23-25 and 27-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status

Claims 12-14, 16, 23-25, 27-34 are pending.

Claims 12-14, 16, 23-25, 27-34 are rejected.

This action will be non-final to address claim 14, 25, 29 and 33, since the new prior art rejection on these claims is not necessitated by amendment.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Double Patenting

1. Claims 12-14, 16, 23-25 and 27-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6,10,11,17,20,22,27-29,31-35 and 37 of copending Application No. 09/842,111 in view of Gonzalez et al (U.S. Patent 6,015,673).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to determining the effectiveness and safety of a 5-fluorouracil based chemotherapeutic regimen by analyzing the mRNA expression of the DPD gene using the same primer sets. These claims differ only in the step of determining the 5-fluorouracil based regimen based upon the DPD mRNA concentration.

Gonzalez teaches a method for determining the level of DPD gene expression in a tissue to determine the safety of a 5-fluorouracil based chemotherapeutic regimen

comprising the steps: (see column 14, lines 41-51, also see column 27, lines 14-27, here the tissue is cultured fibroblasts derived from skin biopsies),

(a) obtaining a sample from a patient (column 14, lines 41-52)

(b) isolating mRNA from the sample (column 14, lines 52-67),

(c) amplifying the mRNA with primers which are substantially identical to SEQ ID NO: 1 and 2 (see column 55, SEQ ID NO: 5)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the DPD analysis method of copending Application 09/842,111 to determining the safety of 5-fluorouracil based chemotherapeutic regimens since Gonzalez states "The method and compositions are useful for identifying persons who are at risk of a toxic reaction to the commonly employed cancer chemotherapy agent 5-fluorouracil (see column 1, lines 8-10)". It is noted that these claims were not subject to restriction from one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 112 – Written Description

3. The rejection of the claims under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 12-13, 16, 23, 24, 27, 28, 31, 32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al (U.S. Patent 6,015,673) in view of Willhauck et al (Biotechniques (1998) 25:656-659) and further in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Stanta et al (Biotechniques (1991) 11(3):303, 306, 308).

Gonzalez teaches a method for determining the level of DPD gene expression in a tissue to determine the safety of a 5-fluorouracil based chemotherapeutic regimen comprising the steps: (see column 14, lines 41-51, also see column 27, lines 14-27, here the tissue is cultured fibroblasts derived from skin biopsies),

(a) obtaining a sample from a patient (column 14, lines 41-52)

(b) isolating mRNA from the sample (column 14, lines 52-67),

(c) amplifying the mRNA with primers which are substantially identical to SEQ ID NO: 1 and 2 (see column 55, SEQ ID NO: 5)

a sequence, SEQ ID NO: 5, which is a sequence substantially identical to the claimed SEQ ID NO: 1 as shown in the alignment below.

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Gonzalez SEQ ID NO: 5 -  GCAAGGAGGGTTTGTCACTG
                         ||||||||||||||||
Claimed SEQ ID NO: 1 AGGAGCAAGGAGGGTTTG
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As the alignment shows, the Gonzalez primer sequence is 14/18 nucleotides identical to the claimed sequence, for a homology over the claimed sequence of 73%.

Further, Gonzalez teaches the complete sequence, 100% identical, of the claimed SEQ ID NO: 1 at nucleotides 37-56 of SEQ ID NO: 1 (see columns 29 and 30) as well as the complete sequence of the claimed SEQ ID NO: 2 at nucleotides 101-120 of SEQ ID NO: 1 (see columns 29 and 30) as well as the complete sequence of the claimed SEQ ID NO: 7 at nucleotides 637-659 of SEQ ID NO: 1 (see columns 29 and 30) as well as the complete sequence of the claimed SEQ ID NO: 8 at nucleotides 702-722 of SEQ ID NO: 1 (see columns 29 and 30).

Further, all of the SEQ ID NO:s are identical to the human DPD sequence disclosed in SEQ ID NO: 1 of U.S. Patent 5,856,454 and are derived from that sequence.

Gonzalez teaches freezing of the sample (see column 25, line 64) as well as fixing of the sample for detection (see column 13, lines 46-53).

Gonzalez teaches isolation of mRNA in the presence of Guanidine, a chaotropic agent (column 14, lines 52-67).

Gonzalez teaches that appropriate samples include any cells from the patient that may express the DPD gene (column 14, lines 41-51).

Gonzalez teaches a threshold for the mutation in which there is a problem tolerating 5-fluorouracil based chemotherapeutic regimens where a 2 fold difference will yield enhanced risk (see column 15, lines 1-11)

Gonzalez does not teach step (d) comparing the amount of DPD mRNA to the amount of mRNA of an internal control gene.

Willhauck teaches comparing the amount of the target gene to an internal control gene (see page 656, columns 1-3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the internal controls of Wilhauck in the method of Gonzalez since Wilhauck states "Taken together our results show that the internal control circumvents a number of inherent problems of alternative controls to assess pre-PCR procedures. The overall RT-PCR assay sensitivity can be reliably evaluated on a per sample basis and the sensitivity limit of the RT-PCR assay can be assessed for every sample. This type of reliability can improve the homogeneity of results from clinical investigations in the future (page 658, column 3 to page 659, column 1)". An ordinary practitioner would have been motivated to use the internal controls of Wilhauck in the method of Gonzalez in order to reliably and sensitively improve the homogeneity of the clinical results.

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers.

Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

While Gonzalez discussed analysis of fixed samples (see column 16, line 63 to column 17, line 5), neither Gonzalez nor Wilhauck teach the standard methods for analysis of RNA from fixed and paraffin embedded samples by PCR.

Stanta teaches a method of extracting RNA from paraffin embedded human tissues comprising:

a) fixing and paraffin embedding tissue samples (see page 304, column 2),

b) isolating mRNA from the FPE tissue sample (see page 304, column 2),

c) amplifying the mRNA by RT-PCR (see page 304, columns 2 and 3).

With regard to the use of a chaotropic agent, Stanta teaches the use of guanidinium thiocyanate in the isolation buffer (see page 304, column 2).

With regard to the temperature ranges given for the isolation, either "about 50 to about 100 C" or "about 75 to about 100 C", Stanta teaches the use of 45 C, which is "about" 50 or "about" 75 C.

With regard to the specific time ranges claimed, of "about 5 to 120 minutes", Stanta teaches a time frame of 6 hours or 360 minutes. In claims where the term "about" is used, 360 minutes is "about" 120 minutes. In the remaining claims, given the absence of any evidence that the time frame has any unexpected properties, an ordinary practitioner would have recognized that the results optimizable variables of time and temperature, could be adjusted to maximize the desired results, whether maximal release of RNA by use of higher temperatures or longer times or maximum speed by use of higher temperatures and shorter times, or maximum care by use of lower temperatures and longer times. These variables are known to directly effect the release of the RNA from the paraffin embedded samples. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific times for amplification was other than routine, that the products resulting from the optimization have any unexpected properties, or that the

results should be considered unexpected in any way as compared to the closest prior art.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the method of Stanta in the method of Gonzalez in view of Wilhauck and further in view of Buck since Stanta teaches "The accessibility of paraffin embedded material for RNA analysis opens the archives of the hospital pathology departments to RNA expression or RNA virus persistence analysis and allows the study of a large number of cases of more or less rare diseases. The method could also be useful for diagnostic procedures with the advantage that it is not necessary to change the usual methods to store human tissues in the hospitals (see page 308, column 2)." Thus, Stanta expressly suggests an advantage in diagnostic applications such as those of Gonzalez, specifically motivating the use of Stanta's method with Gonzalez's diagnostic application by permitting the method to operate with a change of the usual storage method in hospitals.

6. Claims 14, 25, 29 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al (U.S. Patent 6,015,673) in view of Willhauck et al (Biotechniques (1998) 25:656-659) and further in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Stanta et al (Biotechniques (1991) 11(3):303, 306, 308) and further in view of Johnston, et al. (Cancer Research,55(7):1407-12 (April 1995)).

Gonzalez in view of Willhauck et al and further in view of Buck et al and further in view of Stanta et al teach the limitations of claims 12-13, 16, 23, 24, 27, 28, 31, 32 and 34 as discussed above.

Gonzalez in view of Willhauck et al and further in view of Buck et al and further in view of Stanta et al do not teach the use of B-actin as an internal control.

Johnston teaches the use of B-actin as an internal control (see page 1409, right column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use B-actin as a control in the method of Gonzalez in view of Wilhauck and further in view of Buck and further in view of Stanta since Johnston states "TS protein expression was analyzed by Western blot using TS106 monoclonal antibody and densitometry scanning. TS gene expression was measured by PCR analysis using beta-actin as an internal standard." So Johnston teaches that Beta-actin is a desirable internal standard for PCR when analyzing the target enzyme of 5-fluorouracil. Further, Applicant noted in the response filed January 24, 2003, "Finally, to further cement the fact that one of ordinary skill in the art would readily accept the suitability of B-actin as an internal control gene, Applicant herewith provides a list of dozens of the present inventor's own peer-reviewed studies reporting the successful use of B-actin in a large variety of gene expression and tissue applications. Please see Appendix A. (see page 7 of response)." So Applicant has admitted that the ordinary skilled artisan would readily accept B-actin as a known suitable internal control based upon prior art to the current application.

Response to Arguments

7. Applicant's arguments with respect to the claims, filed February 17, 2004, have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
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Art Unit 1637